Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S35	20594	RESTENOSIS	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 17:41
S36	667	VEGF-C or (VEGF NEAR c)or (Vascular ADJ endothelial ADJ growth ADJ factor NEAR C)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 11:02
S37	272	S35 AND S36	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 11:02
S39	32630	ADENOVIRUS	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 11:05
S40	185	S37 AND S39	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 11:06
S41	68	Alitalo NEAR Kari	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 11:22
S42	43	S41 AND S36	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 11:29
S43	1	(S35 AND S36 and S39).CLM.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 11:56
S44	13	(S35 AND S36).CLM.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 11:32
S45	54	(S35 AND S39).CLM.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 11:33
S46	185	S35 AND S36 and S39	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 11:57
S47	2	S35 SAME S36 SAME S39	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 11:58

S48	42	(US-20010007861-$ or US-20030100889-$ or US-20030008824-$ or US-20040105860-$ or US-20030165464-$ or US-20040120950-$ or US-20020094324-$ or US-20030191055-$ or US-20030143209-$ or US-20020061326-$).did. or (US-5652225-$ or US-5747340-$ or US-5766584-$ or US-5785965-$ or US-5792453-$ or US-5830879-$ or US-5840693-$ or US-5869037-$ or US-5962424-$ or US-6033436-$ or US-6100242-$ or US-6121246-$ or US-6130071-$ or US-6174871-$ or US-6177272-$ or US-6263880-$ or US-6290949-$ or US-6329348-$ or US-6331527-$ or US-6372498-$ or US-6403088-$ or US-6335010-$ or US-6284743-$ or US-5851521-$ or US-6793918-$).did. or (WO-9705250-$ or WO-9807832-$ or WO-9833917-$ or WO-9908522-$ or WO-9933485-$). did. or (US-6235713-$ or WO-200024412-$).did.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2004/11/16 11:59
S49	3	S48 AND S46	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2004/11/16 11:59
S50	103764	catheter$3 stent$3	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 14:26
S51	667	VEGF-C or (VEGF NEAR c)or (Vascular ADJ endothelial ADJ growth ADJ factor NEAR C)	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 14:26
S52	303	S50 AND S51	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 14:27
S53	32630	ADENOVIRUS	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 14:27
S54	378	S53 AND S51	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 14:27

S55	236	S50 AND S54	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 14:28
S56	4	S55 AND @PY<="1999"	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 14:30
S57	1	(S50 AND S51 AND S53).CLM.	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 14:34
S58	3	Hammond NEAR Kirk	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 14:34
S59	18	Giordano NEAR Frank	US-PGPUB; USPAT; EPO; JPO; DERWENT	OR	ON	2004/11/16 14:34
S62	48	(("5,087,244") or ("5,631,237") or ("5,653,689") or ("5,674,192") or ("5,679,400") or ("5,697,967") or ("5,700,286") or ("5,707,385") or ("5,713,860") or ("5,749,848") or ("5,776,184") or ("5,776,755") or ("5,779,729") or ("5,785,965") or ("5,792,453") or ("5,795,898") or ("5,799,384") or ("5,800,507") or ("5,824,048") or ("5,830,879") or ("5,924,048") or ("5,932,540") or ("5,935,820") or ("5,994,300") or ("6,040.157")).PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2004/11/16 15:59
S63	2	("6040157").PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2004/11/16 15:59
S64	16	(("6,107,046") or ("6,130,071") or ("6,221,839") or ("6,235,713") or ("6,245,530") or ("6,361,946") or ("6,403,088") or ("6,451,764") or ("6,576,608") or ("6,645,933")).PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2004/11/16 17:51
S65	16	(("20020123481") or ("20020127222") or ("20030091567") or ("20030092604") or ("20030166547") or ("20030166873") or ("20030180294") or ("20040037820")).PN.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	OFF	2004/11/16 17:51

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> d his

     (FILE 'HOME' ENTERED AT 13:30:08 ON 16 NOV 2004)

     FILE 'MEDLINE, CANCERLIT, SCISEARCH, CAPLUS, MEDICONF' ENTERED AT
     13:43:31 ON 16 NOV 2004
L1         28111 S RESTENOSIS
L2         37274 S VEGF-
L3          1621 S VEGF-C OR (VASCULAR ENDOTHELIAL GROWTH FACTOR C)
L4         93540 S ADENOVIR?
L5            33 S L1 (L) L2 (L) L4
L6            14 DUP REM L5 (19 DUPLICATES REMOVED)
L7            14 SORT L6 PY
                 E ALITALIO KARI?/AU
L8           491 S E12
L9             5 S L8 AND L1
L10            5 DUP REM L9 (0 DUPLICATES REMOVED)
L11            5 SORT L10 PY
L12           66 S L3 AND L4
L13           44 DUP REM L12 (22 DUPLICATES REMOVED)
L14            4 S L13 AND (STENT? OR CATHETER?)
L15            4 SORT L14 PY

=> d an ti so au ab pi l11 1-3

L11  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2000:900090  CAPLUS
DN   135:56416
TI   Intravascular adenovirus-mediated VEGF-C gene transfer reduces neointima
     formation in balloon-denuded rabbit aorta
SO   Circulation (2000), 102(18), 2262-2268
     CODEN: CIRCAZ; ISSN: 0009-7322
AU   Hiltunen, Mikko O.; Laitinen, Marja; Turunen, Mikko P.; Jeltsch, Michael;
     Hartikainen, Juha; Rissanen, Tuomas T.; Laukkanen, Johanna; Niemi, Mari;
     Kossila, Maija; Hakkinen, Tomi P.; Kivela, Antti; Enholm, Berndt;
     Mansukoski, Hannu; Turunen, Anna-Mari; Alitalo, Kari;
     Yla-Herttuala, Seppo
AB   Gene transfer to the vessel wall may provide new possibilities for the
     treatment of vascular disorders, such as postangioplasty
     restenosis. In this study, we analyzed the effects of
     adenovirus-mediated vascular endothelial growth factor (VEGF)-C gene
     transfer on neointima formation after endothelial denudation in rabbits.
     For comparison, a second group was treated with VEGF-A adenovirus and a
     third group with lacZ adenovirus. Clin.-grade adenoviruses were used for
     the study. Aortas of cholesterol-fed New Zealand White rabbits were
     balloon-denuded, and gene transfer was performed 3 days later. Animals
     were euthanized 2 and 4 wk after the gene transfer, and intima/media ratio
     (I/M), histol., and cell proliferation were analyzed. Two weeks after the
     gene transfer, I/M in the lacZ-transfected control group was 0.57. VEGF-C
     gene transfer reduced I/M to 0.38. The I/M in VEGF-A-treated animals was
     0.49. The tendency that both VEGF groups had smaller I/M persisted at the
     4-wk time point, when the lacZ group had an I/M of 0.73, the VEGF-C group
     0.44, and the VEGF-A group 0.63. Expression of VEGF receptors 1, 2, and 3
     was detected in the vessel wall by immunocytochem. and in situ
     hybridization. As an addnl. control, the effect of adenovirus on cell
     proliferation was analyzed by performing gene transfer to intact aorta
     without endothelial denudation. No differences were seen in smooth muscle
     cell proliferation or I/M between lacZ adenovirus and 0.9% saline-treated
     animals. Adenovirus-mediated VEGF-C gene transfer may be useful for the
     treatment of postangioplasty restenosis and vessel wall
     thickening after vascular manipulations.

L11  ANSWER 2 OF 5  CAPLUS  COPYRIGHT 2004 ACS on STN
AN   2000:290851  CAPLUS
DN   132:318341
TI   Use of VEGF-C or VEGF-D gene or protein to prevent restenosis
SO   PCT Int. Appl., 61 pp.
     CODEN: PIXXD2
IN   Yla-Herttuala, Seppo; Alitalo, Kari; Hiltunen, Mikko O.;
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Jeltsch, Markku M.; Achen, Marc G.

AB The present invention provides materials and methods for preventing stenosis or **restenosis** of a blood vessel using Vascular Endothelial Growth Factor C (VEGF-C) and/or Vascular Endothelial Growth Factor D (VEGF-D) genes or proteins. A medical device designed to contact a surface of a blood vessel in the course of surgery to treat stenosis of the blood vessel is also claimed, the device characterized by an improvement comprising integrating into the device a composition effective to prevent **restenosis**, said composition comprising at least one anti-**restenosis** agent selected from the group consisting of a VEGF-C polynucleotide, a VEGF-C polypeptide, a VEGF-D polynucleotide, and a VEGF-D polypeptide. The medical device is selected from the group consisting of intravascular stents, intravascular catheters, extravascular collars, elastomeric membranes adapted to cover a surface of an intravascular stent or catheter, and combinations thereof. Also claimed is a kit for treating **restenosis** comprising a container holding at least one anti-**restenosis** agent of the invention and a label attached to or packaged with the container, the label describing use of the compound for prevention of **restenosis** of a blood vessel. The kit further comprises a medical device of the invention.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000024412	A2	20000504	WO 1999-US24054	19991026
WO 2000024412	A3	20000803		
W: AU, CA, CN, JP, NO, NZ				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2340593	AA	20000504	CA 1999-2340593	19991026
EP 1126870	A2	20010829	EP 1999-956559	19991026
EP 1126870	B1	20040908		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NZ 510121	A	20030228	NZ 1999-510121	19991026
AU 768330	B2	20031211	AU 2000-13147	19991026
AT 275417	E	20040915	AT 1999-956559	19991026
NO 2001002017	A	20010626	NO 2001-2017	20010424

L11 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:413877 CAPLUS

DN 138:396218

TI Combination for the treatment of endothelial damage

SO U.S. Pat. Appl. Publ., 11 pp.
CODEN: USXXCO

IN **Alitalo, Kari**; Heldin, Carl Henrik; Leppanen, Olli; Ostman, Arne; Yla-Herttuala, Seppo

AB The invention relates to a combination of (a) an inhibitor of platelet-derived growth factor (PDGF) activity and (b) a vector for vascular endothelial growth factor (VEGF-, especially VEGF-C) gene transfer, a pharmaceutical preparation comprising (a) and (b) in combination together with a pharmaceutically acceptable carrier material; a product comprising (a) and (b) as defined above and optionally a pharmaceutically acceptable carrier material, for simultaneous, chronol. staggered or sep. use; a method of administering or the use of said combination or product for the treatment of endothelial damage; and/or to the use of (a) and (b) for the manufacture of said pharmaceutical preparation or product for the treatment of endothelial damage.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003099687	A1	20030529	US 2002-227081	20020823

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=> d an ti so au ab pi l15 1-4

L15 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:359850 CAPLUS
DN 134:348273
TI Techniques and compositions for treating cardiovascular disease by in vivo gene delivery of a gene encoding an angiogenic protein or peptide
SO PCT Int. Appl., 123 pp.
CODEN: PIXXD2
IN Hammond, H. Kirk; Giordano, Frank J.; Dillmann, Wolfgang H.
AB Methods are provided for treating patients with cardiovascular disease, including heart disease and peripheral vascular disease. The preferred methods of the invention involve in vivo delivery of genes, encoding angiogenic proteins or peptides, to the myocardium or to peripheral ischemic tissue, by introduction of a vector containing the gene into a blood vessel supplying the heart or into a peripheral ischemic tissue.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001034208	A1	20010517	WO 2000-US30345	20001103
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9947541	A1	19991125	AU 1999-47541	19990910
CA 2389524	AA	20010517	CA 2000-2389524	20001103
EP 1225921	A1	20020731	EP 2000-976894	20001103
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003513942	T2	20030415	JP 2001-536204	20001103
US 2003148968	A1	20030807	US 2001-847936	20010503
ZA 2002003303	A	20030526	ZA 2002-3303	20020425

L15 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:868781 CAPLUS
DN 137:363071
TI Techniques and compositions for treating cardiovascular disease by in vivo angiogenic polypeptide-encoding gene delivery
SO PCT Int. Appl., 129 pp.
CODEN: PIXXD2
IN Hammond, H. Kirk
AB Methods are provided for treating patients with cardiovascular disease, including heart disease and peripheral vascular disease. The preferred methods of the invention involve in vivo delivery of genes encoding angiogenic proteins or peptides to the myocardium or to peripheral ischemic tissue, by introduction of a vector containing the gene into a blood vessel supplying the heart or into a peripheral ischemic tissue.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002089856	A1	20021114	WO 2002-US13990	20020503
WO 2002089856	C1	20040401		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 9947541	A1	19991125	AU 1999-47541	19990910
US 2003148968	A1	20030807	US 2001-847936	20010503

L15 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:610064 CAPLUS
DN 139:160389
TI Techniques and compositions for treating cardiovascular disease by in vivo gene delivery of angiogenic peptides and proteins
SO U.S. Pat. Appl. Publ., 51 pp., Cont.-in-part of U.S. Ser. No. 609,080, abandoned.
CODEN: USXXCO
IN Hammond, H. Kirk; Dillmann, Wolfgang; Giordano, Frank J.
AB Methods are provided for treating patients with cardiovascular disease, including heart disease and peripheral vascular disease. The preferred methods of the present invention involve in vivo delivery of genes, encoding angiogenic proteins or peptides, to the myocardium or to peripheral ischemic tissue, by introduction of a vector containing the gene into a blood vessel supplying the heart or into a peripheral ischemic tissue. A kit comprising a gene therapy composition, a device for introducing the composition into a blood vessel or tissue in vivo, and a vasoactive agent is also claimed.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2003148968	A1	20030807	US 2001-847936	20010503
US 5792453	A	19980811	US 1995-485472	19950607
US 6100242	A	20000808	US 1997-722271	19971229
US 6174871	B1	20010116	US 1998-132167	19980810
WO 9940945	A2	19990819	WO 1999-US2702	19990209
WO 9940945	A3	19990930		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9947541	A1	19991125	AU 1999-47541	19990910
WO 2001034208	A1	20010517	WO 2000-US30345	20001103
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
ZA 2002003303	A	20030526	ZA 2002-3303	20020425
WO 2002089856	A1	20021114	WO 2002-US13990	20020503
WO 2002089856	C1	20040401		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004132190	A1	20040708	US 2003-741907	20031219

L15 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:413877 CAPLUS
DN 138:396218
TI Combination for the treatment of endothelial damage
SO U.S. Pat. Appl. Publ., 11 pp.
CODEN: USXXCO
IN Alitalo, Kari; Heldin, Carl Henrik; Leppanen, Olli; Ostman, Arne; Yla-Herttuala, Seppo

AB The invention relates to a combination of (a) an inhibitor of platelet-derived growth factor (PDGF) activity and (b) a vector for vascular endothelial growth factor (VEGF-, especially **VEGF-C**) gene transfer, a pharmaceutical preparation comprising (a) and (b) in combination together with a pharmaceutically acceptable carrier material; a product comprising (a) and (b) as defined above and optionally a pharmaceutically acceptable carrier material, for simultaneous, chronol. staggered or sep. use; a method of administering or the use of said combination or product for the treatment of endothelial damage; and/or to the use of (a) and (b) for the manufacture of said pharmaceutical preparation or product for the treatment of endothelial damage.

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2003099687	A1	20030529	US 2002-227081	20020823

ANSWER 4 OF 14 MEDLINE on STN
AN 2000507205 MEDLINE
TI Intravascular adenovirus-mediated VEGF-C gene transfer reduces neointima formation in balloon-denuded rabbit aorta.
SO Circulation, (2000 Oct 31) 102 (18) 2262-8.
Journal code: 0147763. ISSN: 1524-4539.
AU Hiltunen M O; Laitinen M; Turunen M P; Jeltsch M; Hartikainen J; Rissanen T T; Laukkanen J; Niemi M; Kossila M; Hakkinen T P; Kivela A; Enholm B; Mansukoski H; Turunen A M; Alitalo K; Yla-Herttuala S
AB BACKGROUND: Gene transfer to the vessel wall may provide new possibilities for the treatment of vascular disorders, such as postangioplasty **restenosis**. In this study, we analyzed the effects of **adenovirus**-mediated vascular endothelial growth factor (**VEGF**)-C gene transfer on neointima formation after endothelial denudation in rabbits. For comparison, a second group was treated with **VEGF**-A **adenovirus** and a third group with lacZ **adenovirus**. Clinical-grade **adenoviruses** were used for the study. METHODS AND RESULTS: Aortas of cholesterol-fed New Zealand White rabbits were balloon-denuded, and gene transfer was performed 3 days later. Animals were euthanized 2 and 4 weeks after the gene transfer, and intima/media ratio (I/M), histology, and cell proliferation were analyzed. Two weeks after the gene transfer, I/M in the lacZ-transfected control group was 0. 57+/-0.04. **VEGF**-C gene transfer reduced I/M to 0.38+/-0.02 (P:<0.05 versus lacZ group). I/M in **VEGF**-A-treated animals was 0.49+/-0.17 (P:=NS). The tendency that both **VEGF** groups had smaller I/M persisted at the 4-week time point, when the lacZ group had an I/M of 0.73+/-0.16, the **VEGF**-C group 0.44+/-0.14, and the **VEGF**-A group 0. 63+/-0.21 (P:=NS). Expression of **VEGF** receptors 1, 2, and 3 was detected in the vessel wall by immunocytochemistry and in situ hybridization. As an additional control, the effect of **adenovirus** on cell proliferation was analyzed by performing gene transfer to intact aorta without endothelial denudation. No differences were seen in smooth muscle cell proliferation or I/M between lacZ **adenovirus** and 0.9% saline-treated animals. CONCLUSIONS: **Adenovirus**-mediated **VEGF**-C gene transfer may be useful for the treatment of postangioplasty **restenosis** and vessel wall thickening after vascular manipulations.

L7 ANSWER 5 OF 14 MEDLINE on STN
AN 2003033157 MEDLINE
TI The mechanical study of vascular endothelial growth factor on the prevention of restenosis after angioplasty.
SO Journal of Tongji Medical University = T'ung chi i k'o ta hsueh hsueh pao, (2001) 21 (3) 195-7.
Journal code: 8605495. ISSN: 0257-716X.
AU Liu Q; Lu Z; Zhou H; Yan J; Zhang W
AB The mechanism of vascular endothelial growth factor (**VEGF**) on the prevention of **restenosis** after angioplasty was investigated. The cultured vascular endothelial cells (VEC) were incubated with the conditioned medium (CM) from vascular smooth muscle cells (VSMC) infected with recombinant **adenoviruses** containing the hVEGF165 gene. To observe the effects of **VEGF** on proliferation and NO, ET, 6-keto-PGF1 alpha secretion of VEC, WST-1 method, Griess method and radioimmunoassay were used respectively. The PDGF-B mRNA transcription in VECs was detected by RT-PCR. It was showed that NO, 6-keto-PGF1 alpha and OD value were markedly increased in a dose-dependent manner in the **VEGF**-treated groups as compared with those in the control group, while ET and PDGF-B mRNA were significantly decreased in the **VEGF** -treated groups (P < 0.05 or P < 0.01). **Adenovirus** vector mediated hVEGF165 gene could promote the proliferation of VECs and improve NO, PGI2 secretion, inhibit ET secretion and PDGF-B mRNA transcription in the VECs. The above results offered further theoretical evidence for **VEGF** on the prevention of **restenosis** after angioplasty.

L7 ANSWER 6 OF 14 MEDLINE on STN
AN 2002680810 MEDLINE
TI Clinical trials of gene therapy for atherosclerotic cardiovascular disease.
SO Current opinion in lipidology, (2002 Dec) 13 (6) 653-61. Ref: 59

Journal code: 9010000. ISSN: 0957-9672.

AU Freedman Saul Benedict

AB PURPOSE OF REVIEW: To provide an update on clinical trials of gene therapy for atherosclerotic cardiovascular disease published since 1 August 2001 and summarize the general advantages and potential problems of gene transfer in these disorders. RECENT FINDINGS: There are two major areas in which gene therapy has entered clinical trials. The first is angiogenesis for coronary and peripheral arterial disease. Two relatively small placebo-controlled trials for coronary disease were reported, one using intramyocardial plasmid **VEGF**-2 gene, the other using intracoronary **adenoviral** FGF-4 gene. The **VEGF**-2 study in no-option patients showed reduced angina, and significant improvement in perfusion and function, whereas the FGF-4 study in less severely affected patients showed promising results in some subsets. In peripheral artery disease two phase 1 studies of **adenoviral** NV1FGF and **VEGF** showed some objective improvement in pain, ulcer size and ankle:brachial index in one study and endothelial function in the other. Both **adenoviral** and plasmid **VEGF** gene transfer at angioplasty increased vascularity in a phase 2 double-blind study. The other major area is the prevention of graft disease and **restenosis** using antisense oligodeoxynucleotides. E2F decoy led to a significant reduction in venous graft complications after ex-vivo transfection at the time of coronary bypass surgery, whereas the c-Myc oligodeoxynucleotide was ineffective in preventing in-stent coronary **restenosis**. SUMMARY: There are more reviews of gene therapy for atherosclerosis in the literature than publications with original data or trials, but in the past year the imbalance is being redressed, with some promising results from controlled studies.

L7 ANSWER 7 OF 14 MEDLINE on STN

AN 2002405157 MEDLINE

TI Increased vascularity detected by digital subtraction angiography after VEGF gene transfer to human lower limb artery: a randomized, placebo-controlled, double-blinded phase II study.

SO Molecular therapy : journal of the American Society of Gene Therapy, (2002 Jul) 6 (1) 127-33.
Journal code: 100890581. ISSN: 1525-0016.

AU Makinen Kimmo; Manninen Hannu; Hedman Marja; Matsi Pekka; Mussalo Hanna; Alhava Esko; Yla-Herttuala Seppo

AB Vascular endothelial growth factor (**VEGF**) gene therapy may be useful for the treatment of lower-limb ischemia. The objectives of this study were to evaluate safety and angiographic and hemodynamic responses of local catheter-mediated **VEGF** gene therapy in ischemic lower-limb arteries after percutaneous transluminal angioplasty (PTA). For this study, we recruited patients with chronic lower-limb ischemia and atherosclerotic infrainguinal occlusion or stenosis suitable for PTA. In the study, 18 patients received 2x10(10) plaque-forming units (pfu) **VEGF-adenovirus** (**VEGF**-Ad), 17 patients received **VEGF**-plasmid/liposome (**VEGF**-P/L; 2000 microg of **VEGF** plasmid, 2000 microl of DOTMA:DOPE), and 19 control patients received Ringer's lactate at the angioplasty site. Digital subtraction angiography (DSA) was used to evaluate vascularity before, immediately after, and 3 months after the PTA. Clinical follow-up data, basic laboratory tests, and ankle-brachial index (ABI) were evaluated. Primary endpoint was DSA analysis of vascularity, and secondary endpoints were **restenosis** rate, Rutherford class, and ABI after 3 months follow-up. No major gene transfer-related side effects or differences in laboratory tests were detected between the study groups. However, anti-**adenovirus** antibodies increased in 61% of the patients treated with **VEGF**-Ad. For the primary endpoint, follow-up DSA revealed increased vascularity in the **VEGF**-treated groups distally to the gene transfer site (**VEGF**-Ad P=0.03, VEGFP/L P=0.02) and in the **VEGF**-Ad group in the region of the clinically most severe ischemia (P=0.01). As for the secondary endpoints, mean Rutherford class and ABI showed statistically significant improvements in the **VEGF**-Ad and **VEGF**-P/L groups, but similar improvements were also seen in the control patients. We conclude that catheter-mediated **VEGF** gene therapy is safe and well tolerated. Angiography demonstrated that

VEGF gene transfer increased vascularity after PTA in both **VEGF**-Ad- and **VEGF**-P/L-treated groups.

L7 ANSWER 8 OF 14 MEDLINE on STN
AN 2002296322 MEDLINE
TI Adenovirus encoding vascular endothelial growth factor-D induces tissue-specific vascular patterns in vivo.
SO Blood, (2002 Jun 15) 99 (12) 4434-42.
Journal code: 7603509. ISSN: 0006-4971.
AU Byzova Tatiana V; Goldman Corey K; Jankau Jurek; Chen Juhua; Cabrera Gustavo; Achen Marc G; Stacker Steven A; Carnevale Kevin A; Siemionow Maria; Deitcher Steven R; DiCorleto Paul E
AB The capacity of an **adenovirus** encoding the mature form of vascular endothelial growth factor (**VEGF**)-D, **VEGF**-D Delta N Delta C, to induce angiogenesis, lymphangiogenesis, or both was analyzed in 2 distinct in vivo models. We first demonstrated in vitro that **VEGF**-D Delta N Delta C encoded by the **adenovirus** (Ad-**VEGF**-D Delta N Delta C) is capable of inducing endothelial cell proliferation and migration and that the latter response is primarily mediated by **VEGF** receptor-2 (VEGFR-2). Second, we characterized a new in vivo model for assessing experimental angiogenesis, the rat cremaster muscle, which permits live videomicroscopy and quantitation of functional blood vessels. In this model, a proangiogenic effect of Ad-**VEGF**-D Delta N Delta C was evident as early as 5 days after injection. Immunohistochemical analysis of the cremaster muscle demonstrated that neovascularization induced by Ad-**VEGF**-D Delta N Delta C and by Ad-**VEGF**-A(165) (an **adenovirus** encoding the 165 isoform of **VEGF**-A) was composed primarily of laminin and VEGFR-2-positive vessels containing red blood cells, thus indicating a predominantly angiogenic response. In a skin model, Ad-**VEGF**-D Delta N Delta C induced angiogenesis and lymphangiogenesis, as indicated by staining with laminin, VEGFR-2, and VEGFR-3, whereas Ad-**VEGF**-A(165) stimulated the selective growth of blood vessels. These data suggest that the biologic effects of **VEGF**-D are tissue-specific and dependent on the abundance of blood vessels and lymphatics expressing the receptors for **VEGF**-D in a given tissue. The capacity of Ad-**VEGF**-D Delta N Delta C to induce endothelial cell proliferation, angiogenesis, and lymphangiogenesis demonstrates that its potential usefulness for the treatment of coronary artery disease, cerebral ischemia, peripheral vascular disease, **restenosis**, and tissue edema should be tested in preclinical models.

L7 ANSWER 9 OF 14 MEDLINE on STN
AN 2003258337 MEDLINE
TI Safety and feasibility of catheter-based local intracoronary vascular endothelial growth factor gene transfer in the prevention of postangioplasty and in-stent restenosis and in the treatment of chronic myocardial ischemia: phase II results of the Kuopio Angiogenesis Trial (KAT).
SO Circulation, (2003 Jun 3) 107 (21) 2677-83.
Journal code: 0147763. ISSN: 1524-4539.
AU Hedman Marja; Hartikainen Juha; Syvanne Mikko; Stjernvall Joachim; Hedman Antti; Kivela Antti; Vanninen Esko; Mussalo Hanna; Kauppila Esa; Simula Sakari; Narvanen Outi; Rantala Arto; Peuhkurinen Keijo; Nieminen Markku S; Laakso Markku; Yla-Herttuala Seppo
AB BACKGROUND: Catheter-based intracoronary vascular endothelial growth factor (**VEGF**) gene transfer is a potential treatment for coronary heart disease. However, only limited data are available about local **VEGF** gene transfer given during angioplasty (PTCA) and stenting. METHODS AND RESULTS: Patients with coronary heart disease (n=103; Canadian Cardiovascular Society class II to III; mean age, 58+/-6 years) were recruited in this randomized, placebo-controlled, double-blind phase II study. PTCA was performed with standard methods, followed by gene transfer with a perfusion-infusion catheter. Ninety percent of the patients were given stents; 37 patients received **VEGF** **adenovirus** (**VEGF**-Adv, 2x10(10) pfu), 28 patients received **VEGF** plasmid liposome (**VEGF**-P/L; 2000 microg of DNA with 2000 microL of DOTMA:DOPE [1:1 wt/wt]), and 38 control

patients received Ringer's lactate. Follow-up time was 6 months. Gene transfer to coronary arteries was feasible and well tolerated. The overall clinical **restenosis** rate was 6%. In quantitative coronary angiography analysis, the minimal lumen diameter and percent of diameter stenosis did not significantly differ between the study groups. However, myocardial perfusion showed a significant improvement in the **VEGF**-Adv-treated patients after the 6-month follow-up. Some inflammatory responses were transiently present in the **VEGF**-Adv group, but no increases were detected in the incidences of serious adverse events in any of the study groups. CONCLUSIONS: Gene transfer with **VEGF**-Adv or **VEGF**-P/L during PTCA and stenting shows that (1) intracoronary gene transfer can be performed safely (no major gene transfer-related adverse effects were detected), (2) no differences in clinical **restenosis** rate or minimal lumen diameter were present after the 6-month follow-up, and (3) a significant increase was detected in myocardial perfusion in the **VEGF**-Adv-treated patients.

L7 ANSWER 10 OF 14 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
AN 2003:486451 SCISEARCH
TI Safety and feasibility of catheter-based local intracoronary vascular endothelial growth factor gene transfer in the prevention of postangioplasty and in-stent restenosis and in the treatment of chronic myocardial ischemia - Phase II results of the Kuopio Angiogenesis Trial (KAT)
SO CIRCULATION, (3 JUN 2003) Vol. 107, No. 21, pp. 2677-2683.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 0009-7322.
AU Hedman M; Hartikainen J; Syvanne M; Stjernvall J; Hedman A; Kivela A; Vanninen E; Mussalo H; Kauppila E; Simula S; Narvanen O; Rantala A; Peuhkurinen K; Nieminen M S; Laakso M; Yla-Herttuala S (Reprint)
AB Background - Catheter-based intracoronary vascular endothelial growth factor (**VEGF**) gene transfer is a potential treatment for coronary heart disease. However, only limited data are available about local **VEGF** gene transfer given during angioplasty (PTCA) and stenting.

Methods and Results - Patients with coronary heart disease (n = 103; Canadian Cardiovascular Society class II to III; mean age, 58 +/- 6 years) were recruited in this randomized, placebo-controlled, double-blind phase II study. PTCA was performed with standard methods, followed by gene transfer with a perfusion-infusion catheter. Ninety percent of the patients were given stents; 37 patients received **VEGF** **adenovirus** (**VEGF**-Adv, 2 x 10(10) pfu), 28 patients received **VEGF** plasmid liposome (**VEGF**-P/L; 2000 mug of DNA with 2000 muL of DOTMA: DOPE [1: 1 wt/wt]), and 38 control patients received Ringer's lactate. Follow-up time was 6 months. Gene transfer to coronary arteries was feasible and well tolerated. The overall clinical **restenosis** rate was 6%. In quantitative coronary angiography analysis, the minimal lumen diameter and percent of diameter stenosis did not significantly differ between the study groups. However, myocardial perfusion showed a significant improvement in the **VEGF**-Adv - treated patients after the 6-month follow-up. Some inflammatory responses were transiently present in the **VEGF**-Adv group, but no increases were detected in the incidences of serious adverse events in any of the study groups.

Conclusions - Gene transfer with **VEGF**-Adv or **VEGF** -P/ L during PTCA and stenting shows that (1) intracoronary gene transfer can be performed safely (no major gene transfer - related adverse effects were detected), (2) no differences in clinical **restenosis** rate or minimal lumen diameter were present after the 6-month follow-up, and (3) a significant increase was detected in myocardial perfusion in the **VEGF**-Adv - treated patients.

L7 ANSWER 11 OF 14 MEDLINE on STN
AN 2004410656 IN-PROCESS
TI Experimental study of adenovirus vector mediated-hVEGF165 gene on prevention of restenosis after angioplasty.
SO Journal of Huazhong University of Science and Technology. Medical sciences

= Hua zhong ke ji da xue xue bao. Yi xue Ying De wen ban = Huazhong keji daxue xuebao. Yixue Yingdewen ban, (2004) 24 (2) 132-3, 137.
Journal code: 101169627. ISSN: 1672-0733.

AU Liu Qigong; Lu Zaiying; Yue Yuankun; Lin Li; Zhang Weidong; Yan Jin

AB This study evaluated the effects of **adenovirus** vector mediated human vascular endothelial growth factor-165 (hVEGF165) gene on prevention of **restenosis** after angioplasty. Rabbit models of bilateral carotid artery injury were established by balloon denudation. The recombinant **adenoviruses** containing hVEGF165 cDNA was directly injected into left side of the injured carotid arteries. On day 3 and week 3 after transfection the expression of **VEGF** was observed by RT-PCR and immunohistochemistry. The thrombokinesis, reendothelialization (rET) and intimal hyperplasia in carotid arteries were evaluated by computerized image analysis system 3 weeks after gene transfer. The changes in the **VEGF** gene-treated side were compared with the control side. Our results showed that 3 days and 3 weeks after hVEGF165 gene transfer the **VEGF** mRNA and antigen expression were detected in vivo. 3 weeks after the transfer, the carotid artery rET was markedly better in the **VEGF** gene-treated group compared with the control. The thrombokinesis, intima area/media area (I/M), maximal intimal and medial thicknesses (ITmax and MTmax) demonstrated a statistically significant decrease in arteries treated with **VEGF** gene as compared with the control group. It is concluded that **VEGF** gene transfer could be achieved by intra-arterial injection of recombinant **adenoviruses**. It might accelerate the restoration of endothelial integrity, inhibit thrombokinesis and attenuate intimal hyperplasia in the injured arteries after **VEGF** gene transfer. This procedure could be useful in preventing **restenosis** after angioplasty.

L7 ANSWER 12 OF 14 MEDLINE on STN

AN 2004116508 MEDLINE

TI Oral imatinib mesylate (STI571/gleevec) improves the efficacy of local intravascular vascular endothelial growth factor-C gene transfer in reducing neointimal growth in hypercholesterolemic rabbits.

SO Circulation, (2004 Mar 9) 109 (9) 1140-6.
Journal code: 0147763. ISSN: 1524-4539.

AU Leppanen Olli; Rutanen Juha; Hiltunen Mikko O; Rissanen Tuomas T; Turunen Mikko P; Sjoblom Tobias; Bruggen Josef; Backstrom Gudrun; Carlsson Marianne; Buchdunger Elisabeth; Bergqvist David; Alitalo Kari; Heldin Carl-Henrik; Ostman Arne; Yla-Herttuala Seppo

AB BACKGROUND: Platelet-derived growth factor (PDGF) antagonists have demonstrated beneficial effects on neointima formation, but in studies using PDGF inhibitors and extended follow-up, the lesions reoccur. These findings implicate a need to combine targeting of PDGF with other strategies. Stimulation of reendothelialization by treatment with endothelial cell mitogens of the vascular endothelial growth factor (**VEGF**) family counteracts **restenosis**, but there are also concerns regarding the durability of the effect with this approach. METHODS AND RESULTS: To explore whether a combined use of PDGF antagonist and stimulation of reendothelialization confers better results than each therapy alone, we combined systemic administration of imatinib mesylate (STI571/Gleevec, 10 mg/kg(-1) per d(-1)), a tyrosine kinase inhibitor with activity against PDGF receptors, with local intravascular **adenovirus**-mediated **VEGF**-C gene transfer (1.15x10(10) pfu) in cholesterol-fed, balloon-injured rabbits. Throughout the course of the STI571 therapy, the circulating concentrations were able to suppress PDGF receptor phosphorylation. At 3 weeks, the treatment with STI571 led to a transient decrease in intralesion macrophages and to an increase in intimal smooth muscle cell apoptosis. **VEGF**-C application reduced neointima formation and accelerated reendothelialization. However, none of the therapies alone reduced intimal thickening at a 6-week time point, whereas the combined treatment led to a persistent reduction (55% versus control) in lesion size at this time point. CONCLUSIONS: Our study provides one of the first successful examples of gene therapy combined with a pharmacological treatment to modulate 2 distinct ligand-receptor signaling systems and suggests combination of local **VEGF**-C gene therapy with systemic inhibition of PDGF signaling as a novel principle to prevent intimal hyperplasia after vascular manipulations.

Kaushal, Sumesh

From: Kaushal, Sumesh
Sent: Tuesday, November 16, 2004 1:37 PM
To: STIC-Biotech/ChemLib
Subject: 09427657: SEQ and interference search

09427657: SEQ and interference search

SEQ ID NO:1 (352-1608) DNA ~1350nt long
SEQ ID NO:2 PRT 419aa long

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